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Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review

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Aims For patients undergoing cardiac resynchronization therapy (CRT) with implantable cardioverter-defibrillator (ICD; CRT-D), the effect of an improvement in left ventricular ejection fraction (LVEF) on appropriate ICD therapy may have significant implications regarding management at the time of ICD generator replacement.

Methods and results We conducted a meta-analysis to determine the effect of LVEF recovery following CRT on the incidence of appropriate ICD therapy. A search of multiple electronic databases identified 709 reports, of which 6 retrospective cohort studies were included ($n = 1740$). In patients with post-CRT LVEF $\geq$35% (study $n = 4$), the pooled estimated rate of ICD therapy (5.5/100 person-years) was significantly lower than patients with post-CRT LVEF <35% [incidence rate difference (IRD): −6.5/100 person-years, 95% confidence interval (95% CI): −8.8 to −4.2, $P < 0.001$]. Similarly, patients with post-CRT LVEF $\geq$45% (study $n = 4$) demonstrated lower estimated rates of ICD therapy (2.3/100 person-years) compared with patients without such recovery (IRD: −5.8/100 person-years, 95% CI: −7.6 to −4.0, $P < 0.001$). Restricting analysis to studies discounting ICD therapies during LVEF recovery (study $n = 3$), patients with LVEF recovery ($\geq$35 or $\geq$45%) had significantly lower rates of ICD therapy compared with patients without such recovery (P for both <0.001). Patients with primary prevention indication for ICD, regardless of LVEF recovery definition, had very low rates of ICD therapy (0.4 to 0.8/100-person years).

Conclusion Recovery of LVEF post-CRT is associated with significantly reduced appropriate ICD therapy. Patients with improvement of LVEF $\geq$45% and those with primary prevention indication for ICD appear to be at lowest risk.

Keywords Resynchronization • Ventricular tachyarrhythmia • Meta-analysis

Introduction

Cardiac resynchronization therapy (CRT) has become a standard therapy in appropriately selected patients with left ventricular systolic dysfunction (LVSD), symptomatic heart failure, and electrical dyssynchrony. Resynchronization of the failing heart leads to favourable ventricular reverse remodelling characterized by reduced LV volumes and improved LV ejection fraction (LVEF), ultimately translating to significant reductions in morbidity and mortality.[1] In conjunction with CRT, many patients undergo implantation of an implantable cardioverter-defibrillator (ICD; CRT-D) given its efficacy in the prevention of sudden cardiac death (SCD) in patients with systolic heart failure.[2]

Given the salutary effects of CRT on LV function, and the established relationship between risk of ventricular tachyarrhythmia

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(VTA) and LVEF, there has been significant interest regarding the impact of CRT-induced improvement in LV function and risk of VTA.[3–9] To the extent that contemporary ICD implantation guidelines rely on LVEF assessment,[10] the impact of CRT and LVEF improvement on VTA risk has substantial clinical and cost-effectiveness implications at the time of ICD generator replacement. In addition, identification of patients likely to experience CRT-related improvement in LVEF and possibly attenuated future risk of VTA may further impact the selection of CRT-pacing (CRT-P) vs. CRT-D.

To date, there are no prospective, randomized studies assessing the efficacy of ICD implantation in patients with post-CRT LVEF recovery. Given the clinical equipoise and the expanding population of patients for whom this decision-making will be impactful, we conducted a meta-analysis of cohort studies assessing the incidence of VTA in patients with LVEF recovery following CRT. We report subset analyses stratified by the degree of LVEF improvement, the timing of VTA assessment in relation to LVEF recovery, and the index indication for ICD implantation.

Methods

Search strategy

We performed an electronic literature search of MEDLINE (1948 to December 2014), MEDLINE In-Process and Other Non-Indexed Citations, Cumulative Index to Nursing and Allied Health Literature, the Cochrane Database of Systematic Reviews (Fourth Quarter, 2010), the American College of Physicians Journal Club (1991 to November 2011), Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials using the following search terms: biventricular, resynchronization, arrhythmia, recovery, improvement, ICD, defibrillator, and responder (see Supplementary material online, *Appendix S1*). We also hand searched the bibliographies of all review articles published in the past 5 years discussing ICD therapy and CRT.

We included published data from retrospective cohort studies assessing ICD therapy in patients with and without LVEF improvement following CRT. We selected studies which defined comparator groups using discrete LVEF cutpoints (e.g. ≥35%) and assessed the incidence of appropriate ICD therapies [defined as patients with appropriate shock or anti-tachycardia pacing (ATP)]. In a subgroup analysis, we analysed studies in which ICD therapies were assessed after follow-up LVEF assessment (i.e. ICD therapies occurring between CRT implant and follow-up LVEF assessment were not counted in the primary endpoint). Reports in which comparator groups were not defined by discrete LVEF cutpoints (CRT responder vs. non-responder) were excluded, as were studies including patients with both CRT-D and CRT-P.

Data extraction

Two investigators (N.A.C. and A.R.) independently extracted data on patient and study characteristics, outcomes, and study quality for each trial. The Meta-analysis of Observational Studies in Epidemiology checklist for observational studies was utilized for study selection and review.[11] Study quality was assessed qualitatively using the Downs and Black checklist.[12] Disagreements were resolved by consensus (N.A.C and A.R.).

Data analysis

The estimated incidence rates for groups of interest were calculated using the number of patients with appropriate ICD therapies and the person-years of follow-up derived from subgroup *N* and median follow-up, as previously described.[13] Estimated incidence rates are reported as per 100 person-years. Median follow-up time was defined as the time of assessment of ICD therapies which began (i) immediately following CRT implant in three studies[3,8,9] and (ii) after follow-up LVEF assessment in three studies (i.e. studies blanked ICD therapies prior to follow-up LVEF assessment).[4–6] The IRD between groups was calculated using the inverse variance fixed-effects model in StatsDirect (StatsDirect Ltd, London, England). A fixed-effect model was selected to minimize instability related to estimating random, study-level effects given the limited number of studies. A sensitivity analysis was performed using a DerSimonian-Laird random-effects model (StatsDirect Ltd) with no change to the study results. Heterogeneity was quantified using the I^2 statistic (a value of 0% indicates minimal heterogeneity).[14] Bias was assessed using the Egger's regression test.[15] Pre-specified subgroup analysis was performed for studies which discounted ICD therapies occurring prior to post-CRT LVEF reassessment.

Results

Search results

The initial search yielded 709 reports, of which 6 [3–6,8,9] met inclusion criteria (*Figure 1*). Five of the six studies selected were retrospective, cohort studies[3,4,6,8,9] whereas one was a *post hoc* analysis of a randomized controlled trial (Multicenter Automatic Defibrillator Implantation Trial, MADIT-CRT).[5] The method of ICD therapy adjudication was described in all but one study,[8] although assessment was blinded in only one study (Supplementary material online, *Table S1*).[5] Four studies described a frequency protocol for endpoint assessment.[3,5,6,9] While all studies clearly define and report the endpoint of interest (appropriate ICD therapies), only two studies additionally reported incident inappropriate therapies.[5,9]

Selected studies included a total of 1740 patients with relatively advanced LVSD (average or median LVEF range: 20–29%; *Table 1*). Of studies reporting New York Heart Association (NYHA) class,[3,4,6,9] there was a range of heart failure (HF) symptom severity (45–86% NYHA III). The prevalence of AF varied across studies (10–40%) as did use of anti-arrhythmic medications (8–29%). Of studies reporting the index indication for ICD implantation a significant majority of patients (≥75% of each study population) underwent implant for primary prevention. The timing of echocardiographic assessment for delineation of LVEF recovery was heterogeneous and ranged from 4 to 20 months post-implant. With respect to stratification of LVEF recovery, two studies assessed modest recovery of LV function (LVEF ≥35%),[6,9] two studies assessed the impact of significant LVEF recovery (LVEF ≥45–50%),[3,4] and two studies stratified at both levels of LVEF (modest and significant recovery).[5,8] All studies utilized the presence of ATP or defibrillator therapy, as reviewed by electrophysiologists, to define appropriate ICD therapy although programming details were only available in a minority of studies,[5,6] and not standardized. The median follow-up range for VTA assessment was 1.5–3 years (3719 estimated person-years of follow-up). Finally, three studies[4–6] assessed ICD therapies after post-CRT LVEF assessment (i.e. ICD therapies between CRT

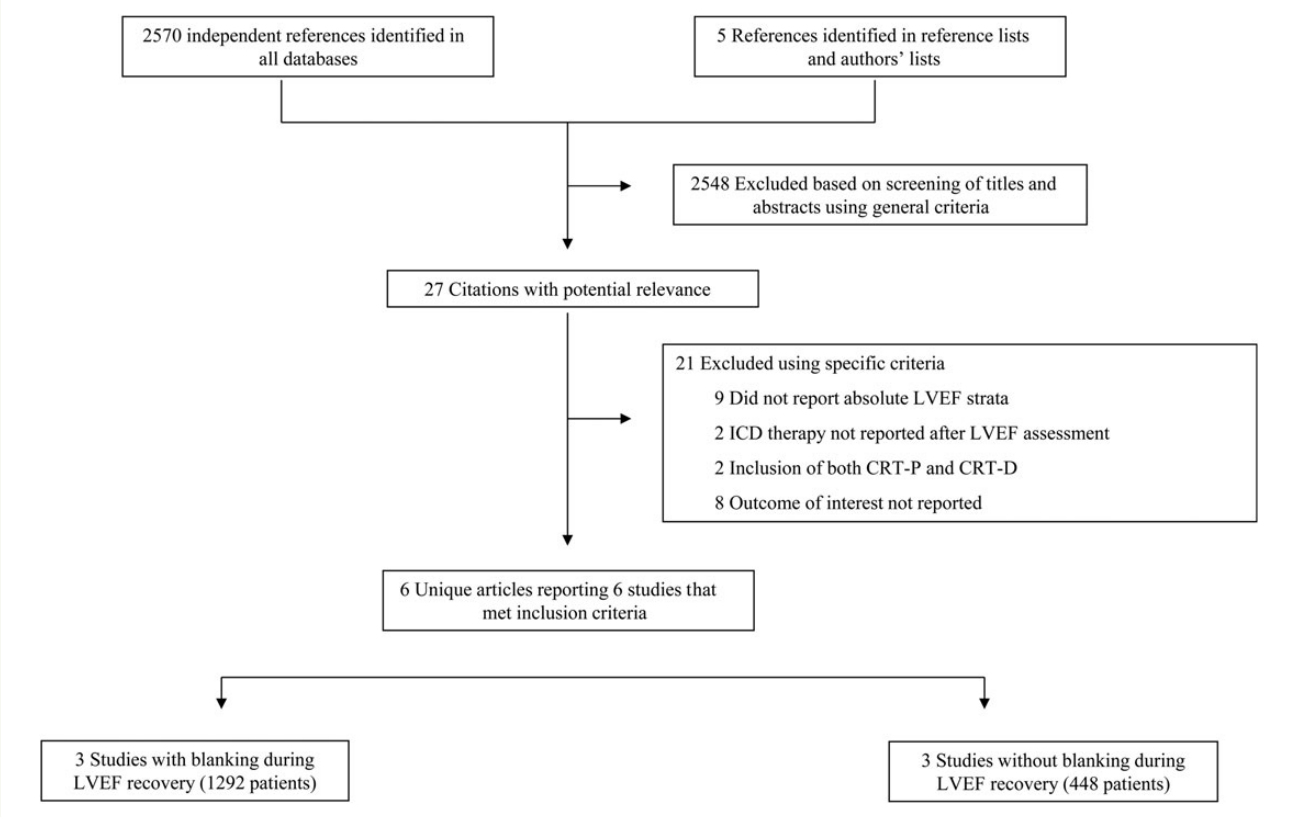


Figure 1 Search strategy.

implant and echocardiographic follow-up were blanked), whereas the remainder assessed ICD therapies from the time of CRT implant.

Implantable cardioverter-defibrillator therapies associated with left ventricular ejection fraction recovery ≥35% after cardiac resynchronization therapy

Of studies reporting appropriate ICD therapies in patients with modest LVEF recovery (≥ vs. <35%; study $n = 4$),[5,6,8,9] the estimated pooled incidence rate of appropriate therapy in patients with post-CRT LVEF ≥35% was 5.4/100 person-years and significantly lower than in patients without such recovery [(IRD): −6.1/100 person-years, 95% confidence interval (CI): −8.2 to −4.0, $P < 0.001$] (*Figures* 2*A* and 3). There was no identified heterogeneity across studies ($I^2 = 0\%$) and no evidence of systematic bias (Egger $P = 0.74$). In subgroup analysis of studies in which ICD therapies prior to follow-up LVEF assessment were blanked (study $n = 2$),[5,6] the absolute pooled rate of appropriate ICD therapy was 5.6/100 person-years in patients with LVEF ≥35% and significantly lower than patients with post-CRT LVEF <35% (IRD: −7.5/100 person-years, 95% CI: −11.4 to −3.6, $P < 0.001$; *Figures* 2*B* and 3). Only one study reported the relative timing of ICD therapy in each LVEF strata.[6] Of patients with LVEF recovery to ≥35% ($n = 57$), 38% of appropriate ICD therapies occurred in the first 12 months following CRT implant (5 of 13). This proportion was generally similar to patients without LVEF recovery (<35%; $n = 212$), for whom 31% of appropriate ICD therapies occurred in the first year after CRT (25 of 81).

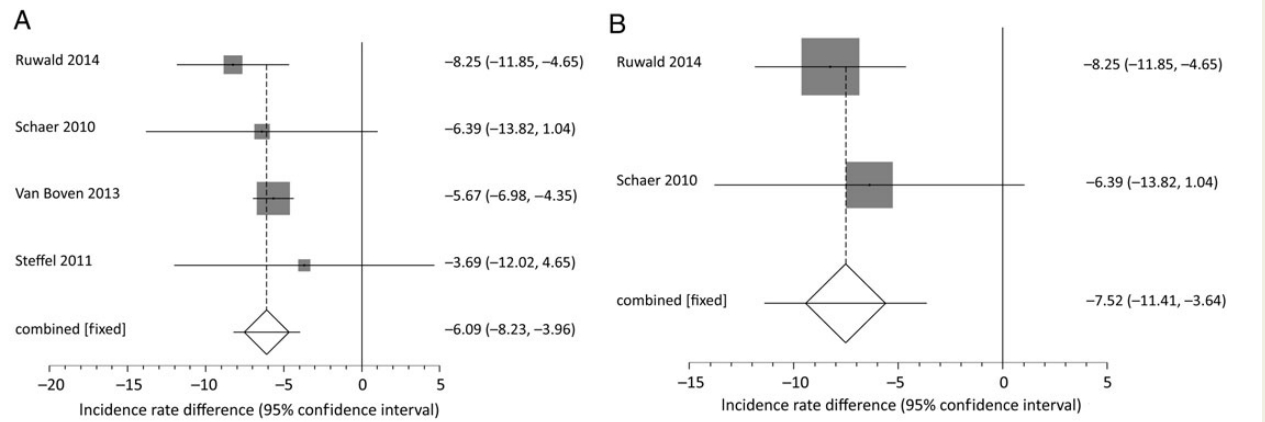
Implantable cardioverter-defibrillator therapies associated with left ventricular ejection fraction ≥45% after cardiac resynchronization therapy

Of studies which assessed ICD therapies in patients with vs. without significant LVEF improvement (LVEF ≥45–50%),[3–5,8] the absolute pooled rate of appropriate ICD therapies in patients with LVEF ≥45% was 2.3/100 person-years and significantly lower than in patients without LVEF such improvement (IRD: −5.9, 95% CI: −7.6 to −4.1, $P < 0.001$; *Figures* 3 and 4*B*). There was minimal heterogeneity or bias ($I^2 = 0\%$, Egger $P = 0.39$). Of studies which blanked ICD therapies prior to LVEF assessment (study $n = 2$),[4,5] the absolute pooled rate of ICD therapy in patients with significant LVEF recovery was very low (1.7/100 person-years) and significantly lower than in patients without such recovery (IRD: −5.5, 95% CI: −7.5 to −3.5, $P < 0.001$; *Figures* 3 and 4*B*).

Table 1 Baseline characteristics and endpoint adjudication of included studies

	Schaer 2010	Manfredi 2013	Ruwald 2015	Steffel 2011	Van Boven 2013	Garcia-Lunar 2014
N	270	270[a]	752	110	142	196
Age, years	60.9 (11.1)	71 [64–77]	65 (2)	63.1 (10.9)	69 [61–74]	63 (2)
Women, (%)	23	28	25	18	30	15
LVEF baseline, %	22 (5)	20 [15–25]	29 (1)	26 (8)	20 [18–25]	26 (1)
ICD indication, (%)						
Primary	75	100	93		100	81
Secondary	25	0	7	—	0	19
Ischaemic cardiomyopathy, %	48	59	55	44	53	46
NYHA class, %						
II	27	2			52	21
III	68	86	—		45	76
IV	5	12		—	3	3
Atrial fibrillation, %	21	40	10	14	26	—
QRSd, ms	165 (28)	154 [133–174]	159 (4)	154 (29)	71% with QRS >150	161 (5)
Medications						
β-blocker	77	97	94		91	87
Digoxin	28	—	27		—	—
ACEi/ARB	94	84	95		98	85
AADs	29	18	8	—	—	37
Time of LVEF assessment post-CRT implant, months	20 (15)	7 [7–13]	12	6.4 (2.7)	4	12
LVEF recovery definition	≥ vs. <35%	≥ vs. <45%	>50%, 36–50%, ≤35%	≥ vs. <35%, ≥ vs. <45%	≥ vs. <35%	≥ vs. <45%
% with LVEF recovery	21	14	86 (>35%) 7 (>50%)	46 (>35%) 17 (>45%)	30	26
Definition of ICD therapy	ATP or shock in VT/VF zone	ATP or shock in VT/VF zone	ATP or shock in VT/VF zone	ATP or shock in VT/VF zone	ATP or shock in VT/VF zone	ATP or shock in VT/VF zone
	VT Zone 1° prevention 175–180 b.p.m. with initial ATP					
	2° prevention 155–160 b.p.m. with initial ATP		VT Zone 180–250 b.p.m. with initial ATP			
Programming details	VF Zone DCCV at ≥210 b.p.m.	Provider Discretion	VF Zone DCCV at ≥250 b.p.m.	Provider Discretion	Provider Discretion	Provider Discretion
Median follow-up, years[b]	1.9	1.5	2.2	2.1	3	2.5
Blanking[c] of ICD therapies prior to LVEF reassessment	Yes	Yes	Yes	No	No	No

Data are presented as either average (standard deviation) or median [interquartile range] as appropriate.
LVEF, left ventricular ejection fraction; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association class; QRSd, QRS duration; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AADs, anti-arrhythmic drugs (Vaughn-Williams Class III); CRT, cardiac resynchronization therapy; ATP, anti-tachycardia pacing; VT/VF, ventricular tachycardia/ventricular fibrillation; b.p.m., beats per minutes; DCCV, direct current cardioversion.
[a]Baseline characteristics are provided for subgroup of population ($N = 289$), whereas the landmark population of interest utilized in meta-analysis was smaller ($N = 270$).
[b]Median follow-up is for time after follow-up LVEF assessment in studies which blank for ICD therapies prior to LVEF assessment. For studies without blanking, follow-up time is defined after CRT implant.
[c]Blanking refers to studies which did not count ICD therapies occurring between CRT implant and time of LVEF reassessment.



Study	IRD	95% CI	% Weight
Ruwald 2014	−8.25	−11.85 to −4.65	18.4
Schaer 2010	−6.39	−13.82 to 1.04	11.8
Van Boven 2013	−5.67	−6.98 to -4.35	63.0
Steffel 2011	−3.69	−12.02 to 4.65	6.8
Pooled	−6.09	−8.23 to -3.96	P<0.001

Study	IRD	95% CI	% Weight
Ruwald 2014	−8.25	−11.85 to −4.65	60.9
Schaer 2010	−6.39	−13.82 to 1.04	39.1
Pooled	−7.52	−11.41 to -3.64	P<0.001

Figure 2 Incidence rate difference of appropriate implantable cardioverter defibrillator therapy in patients with post-cardiac resynchronization therapy left ventricular ejection fraction recovery to ≥35%. Incidence rate difference (IRD) of patients with appropriate implantable cardioverter defibrillator therapy and post-cardiac resynchronization therapy left ventricular ejection fraction ≥35% compared with patients with post-cardiac resynchronization therapy left ventricular ejection fraction <35% for all studies (*A*) and for studies which blanked implantable cardioverter defibrillator therapies occurring between cardiac resynchronization therapy implant and follow-up left ventricular ejection fraction assessment (*B*). Shown are pooled incidence rate differences. CI, confidence interval.

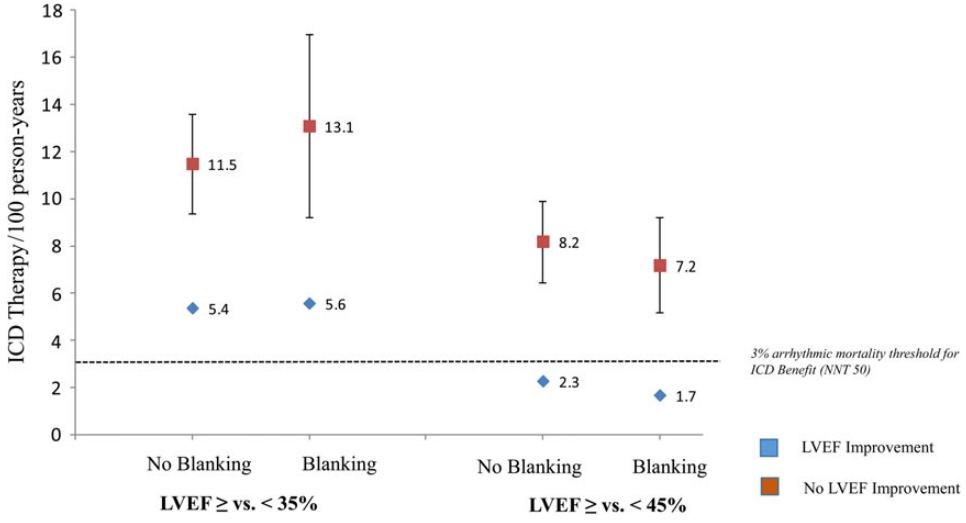
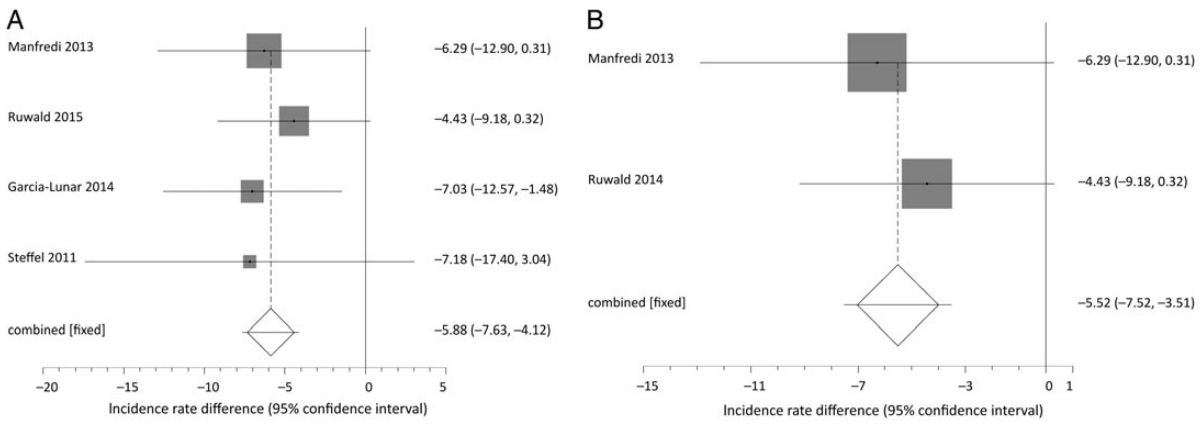


Figure 3 Summary of appropriate implantable cardioverter defibrillator (ICD) therapy stratified by left ventricular ejection fraction improvement and presence of post-implant blanking. Shown are the absolute pooled rates of appropriate implantable cardioverter defibrillator therapy for patients with post-implantable cardioverter defibrillator left ventricular ejection fraction (LVEF) recovery (blue diamond; ≥35 or 45% where indicated) as well as the pooled estimated incidence rate difference (with 95% confidence interval) in patients without such recovery. Groups are stratified by the presence or absence of blanking implantable cardioverter defibrillator therapies occurring between cardiac resynchronization therapy implant and follow-up left ventricular ejection fraction assessment. Dashed line indicates the estimated annual arrhythmic mortality (3%) associated with a number needed to treat (NNT) effectiveness estimate of 50 for implantable cardioverter-defibrillator implant (see text).



Study	IRD	95% CI	% Weight
Manfredi 2013	−6.29	−12.9 to 0.31	44.6
Ruwald 2014	−4.43	−9.18 to 0.32	32.1
Garcia-Lunar 2014	−7.03	−12.57 to −1.48	18.1
Steffel 2011	−7.18	−17.4 to 3.04	5.2
Pooled	−5.88	−7.63 to -4.12	P<0.001

Study	IRD	95% CI	% Weight
Manfredi 2013	−6.29	−12.9 to 0.31	58.2
Ruwald 2014	−4.43	−9.18 to 0.32	41.8
Pooled	−5.52	−7.52 to −3.51	P<0.001

Figure 4 Incidence rate difference of appropriate implantable cardioverter defibrillator therapy in patients with post-cardiac resynchronization therapy left ventricular ejection fraction recovery to ≥45%. Incidence rate difference of patients with appropriate implantable cardioverter defibrillator therapy and post-cardiac resynchronization therapy left ventricular ejection fraction ≥45% compared with patients with post-cardiac resynchronization therapy left ventricular ejection fraction <45% for all studies (*A*) and for studies which blanked implantable cardioverter defibrillator therapies occurring between cardiac resynchronization therapy implant and follow-up left ventricular ejection fraction assessment (*B*). Shown are pooled incidence rate differences. CI, confidence interval; IRD, incidence rate difference.

Implantable cardioverter-defibrillator therapies stratified by index implantable cardioverter-defibrillator indication

Of studies stratifying patients by post-CRT LVEF ≥ vs. <35%, one provided detailed information regarding ICD therapies in patients with a primary prevention indication (ICD therapies blanked in first year after CRT)[6] and another exclusively enrolled patients with a primary prevention indication (ICD therapies counted immediately post-CRT).[9] The pooled absolute rate of appropriate ICD therapy in patients with post-CRT LVEF ≥35% was very low (0.4/100 person-years) compared with patients without such recovery (9.0/100 person-years). Only one study stratifying patients by post-CRT LVEF recovery to ≥45% vs. <45% reported ICD rates for patients with primary prevention ICD which were numerically lower in patients with LVEF recovery (0.8 vs. 5.5/100 person-years).[4]

Discussion

This meta-analysis represents the first systematic synthesis of available cohort studies assessing the incidence of VTA in patients undergoing CRT with LVEF recovery. The central findings of this study are: (i) the presence of LVEF recovery following CRT is associated with significant reduction in the risk of VTA compared with patients without such recovery. (ii) The reduction of VTA with LVEF recovery was present regardless of the context of ICD therapy assessment (post-implant vs. post-LVEF reassessment). (iii) Patients with recovery of LVEF ≥45% and those with LVEF recovery in the context of a primary prevention ICD indication were at particularly low risk.

The incremental efficacy of ICD therapy over CRT-P alone has never been directly established as highlighted by previous meta-analysis[16] and consensus guidelines.[10] In the only randomized controlled trial to include both CRT-P and CRT-D arms (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure, COMPANION), both CRT modes were associated with significant reduction in the composite endpoint of death or HF hospitalization in an advanced HF population (86% NYHA class III).[17] Over a relatively short duration of follow-up (mean 14 months), CRT-D therapy demonstrated a statistically significant 36% relative reduction in mortality compared with optimal medical therapy (OMT), whereas CRT-P was associated with a numeric trend to reduced mortality (24% risk reduction, $P = 0.06$). In *post hoc* analysis, CRT-D (but not CRT-P) was associated with a significant reduction in SCD compared with OMT.[18] In contrast to the null findings of COMPANION, longer-term follow-up of the CARE-HF study (mean follow-up: 37 months) identified a significant, delayed reduction in SCD with CRT-P alone (vs. OMT) in patients with similarly advanced HF (46% risk reduction, $P = 0.006$).[19]

The combination of these findings—the early reduction in SCD with CRT-D alone and the delayed SCD reduction of CRT-P vs. OMT—has led several to suggest an anti-arrhythmic benefit associated with the salutary effects of CRT on LV function, NYHA class, and autonomic function.[20–22] Indeed, several studies have

demonstrated an association between CRT response (defined by improvement in LVEF, reduction in LV volume, and/or NYHA class) and a reduced risk of VTA compared with CRT non-responders.[21,22] In some studies, the reduction in VTA was apparent within 1 month of implant.[21] In addition to VTA reduction, others have suggested that normalization of LVEF following CRT is associated with normalization of survival compared with age- and gender-matched controls.[23]

Left ventricular ejection fraction recovery after cardiac resynchronization therapy: impact on appropriate implantable cardioverter-defibrillator therapies

While response to CRT has been variably defined,[24] given the focus of contemporary ICD implant guidelines on absolute LVEF,[10] we restricted our analysis to studies comparing VTA in groups defined by discrete post-CRT LVEF cutpoints. In the studies included here (baseline average LVEF 20–29%), nearly two-thirds of patients demonstrated post-CRT LVEF ≥35% (63%) and 10% had LVEF recovery to ≥45% after implant. And while the incidence of LVEF recovery is related to the prevalence of baseline predictors of LV reverse remodelling [e.g. female gender, non-ischaemic aetiology, left bundle branch abnormality (LBBB), QRS ≥ 150 ms], the rates reported in this analysis are similar to previous reports of significant LVEF recovery to ≥45% (frequency range: 7–14%)[25,26] and LVEF recovery to ≥35% (frequency range: 43–74%)[22,26] following CRT.

There are several issues to consider in the interpretation and generalization of these data. First, there was a significant variation in the timing of LVEF reassessment (range: 4–20 months). In studies in which LVEF reassessment was relatively early, we cannot rule out the possibility of subsequent LVEF improvement in patients categorized as LVEF non-responders or the impact of continued LV reverse remodelling in LVEF responders.[27] Secondly, the inclusion of studies which discounted ICD therapy between implant and LVEF reassessment importantly allowed for the consideration of a non-linear distribution of SCD risk following CRT. Given the relationship between lower LVEF and increased VTA risk, inclusion of studies that did not perform blanking would only bias the IRD towards the null to the extent that ICD therapies are occurring early post-implant in eventual CRT responders. Thirdly, the majority of patients across studies had a primary prevention indication for ICD implant and overall rates of ICD therapy are likely to be higher in a secondary prevention population. In the three studies which allowed for stratification by ICD indication,[4,6,9] regardless of LVEF recovery definition (≥35 or ≥45%), patients with a primary prevention indication were at very low risk of ICD therapy post-CRT (0.4–0.8/100 person-years). Fourthly, device programming was only reported in two studies[5,6] and we cannot rule out heterogeneity introduced by the lack of standardization in ICD programming or provide sub-analysis regarding the incidence of VTA not meeting criteria for ICD therapy or those terminated with ATP alone. In addition, the magnitude of ICD therapy rates was likely higher than contemporary practice considering that all studies were performed prior to the recent demonstration of the salutary effects of more liberal ICD programming.[28] Finally, given the absence of individual patient data available in this meta-analytic synthesis, we are unable to adjust for possible confounders which may have been independently related to both LV reverse remodelling (improved LVEF) and VTA risk. For example, in the MADIT-CRT substudy included in this meta-analysis,[5] LBBB and gender were associated with both LVEF normalization and reduced VTA risk, although importantly the relationship between LVEF recovery and reduced VTA remained significant even with adjustment for these and other covariates associated with LVEF recovery.

Role of implantable cardioverter-defibrillatorin cardiac resynchronization therapy: balancing efficacy, cost-effectiveness, and morbidity

In patients undergoing CRT, there remains no consensus recommendation regarding the role of continued ICD therapy in patients with evidence of LVEF recovery. Beyond questions of efficacy, additional implications of continued ICD therapy in patients undergoing CRT include short- and long-term ICD device complications,[29,30] cost-effectiveness of CRT-D vs. CRT-P therapy,[31] and the morbidity and clinical implications of inappropriate ICD therapy.[32] The ever-increasing incidence of HF and patients eligible for CRT,[1] coupled with the contemporary predominance of CRT-D implantation amongst CRT implants (e.g. 80% in the United States, >75% globally),[2,33] suggests that the population of patients for whom this decision-making will be impactful will only increase with time.

The efficacy of ICD therapy reflects the integration of the absolute and relative prevalence of SCD as well as the temporal distribution of SCD risk. Given the time-dependent influence of CRT on LV reverse remodelling and heart failure status, CRT may modify all three of these parameters. With respect to absolute risk, these data support a significant absolute reduction in VTA to clinically significant low rates with LVEF recovery post-CRT (2.3 and 5.6/100 person-years for LVEF recovery of ≥45 and ≥35%). The absolute SCD risk is likely even lower than the rates identified given that only a fraction of appropriate ICD therapies would have aborted sudden death.[34] The efficacy of ICD therapy in CRT patients with LVEF recovery must additionally integrate competing mechanisms of death. Age, NYHA class, as well as non-cardiac comorbidities have each been shown to impact the distribution of modes of death and by extension ICD efficacy in patients with systolic failure.[35] In the largest, real-world cohort assessing mode of death following CRT-D[36] annual mortality was ~3% (annualized over 8-year follow-up) which was similar to randomized controlled trials of CRT with mild HF (e.g. MADIT-CRT)[37] but lower than trials of more advanced HF (COMPANION, CARE-HF; annual mortality 9–12%).[17,19] In this real-world CRT cohort, the most common mode of death was HF mortality (43% of all deaths; 3%/year) followed by non-cardiac death (31% of all deaths; 2.3%/year). The incidence of sudden death was very low (7% of all deaths; 0.5%/year) which may be attributable both to difficulties in adjudication in real-world cohorts as well as the possibility that effective ICD therapy shifted the mode of death (e.g. from SCD to HF-related).

Decision-making regarding ICD therapy in CRT must also reflect cost-effectiveness considerations as well as the risks associated with ICD implantation. As shown previously in the CARE-HF cohort,[31] when compared with medical therapy, the incremental cost of

CRT-D per life year gained is significantly higher than that of CRT-P (e.g. for 65-year-old patient: €35 864 vs. €7011). The cost-effectiveness discrepancy in patients with LVEF recovery may be even higher given that the efficacy of ICD therapy in this population is likely lower than that identified in CARE-HF. Additional risk-benefit considerations must also account for the incidence of ICD lead failure/malfunction (15% over 3 years),[30] complications associated with device replacement,[29] and the morbidity associated with inappropriate ICD therapy including worsened quality-of-life and clinical outcome.[32] Only a minority of studies[5,9] included in this meta-analysis provided discrete data regarding inappropriate ICD therapies or device-related morbidity which would only underestimate the risks associated with ICD therapy in patients with LVEF recovery.

Clinical implications

While the definition of clinically meaningful survival benefit with ICD therapy remains controversial,[34] previous investigators have used a number needed to treat (NNT) threshold of 50.[38] As shown recently, assuming a relative risk reduction in SCD of ~40% with ICD therapy (qualitatively similar to SCD risk reduction of CRT-D vs. OMT in COMPANION),[18] the baseline risk of SCD would need to exceed 3% per year to reach the NNT threshold of 50.[38] By this admittedly crude approach, and taking the extreme that 100% of appropriate ICD therapy was associated with aborted SCD, patients with LVEF recovery to ≥45% and those with a primary prevention ICD indication and LVEF recovery (≥35 or ≥45%) in this meta-analysis would not warrant replacement of ICD at the time of generator replacement. Indeed, recent appropriate-use guidelines, acknowledging the lack of supportive data, suggest deferral of continued ICD therapy *may be appropriate* in patients with CRT implanted for primary prevention with evidence for LVEF recovery (>35%) and no appropriate ICD therapy during the initial implant duration.[39] Counterbalancing this perspective are the recent contemporary demonstrations of worsened survival associated with CRT-P compared with CRT-D even with guideline-directed implantation of CRT-P in 'low VTA risk' patients (female, non-ischaemic, and no prior VTA).[40,41] Ultimately, given the heterogeneity and dearth of data highlighted in this meta-analysis, a randomized controlled assessment of deferred ICD therapy in post-CRT patients at low absolute risk for VTA may be warranted.

Study limitations

There are several limitations inherent to this analysis, many of which have already been reviewed. Additionally, given the granularity of the data we were unable to assess the impact of NYHA improvement which has been established as a risk factor for appropriate ICD therapy and possible modifier of ICD efficacy.[34] Secondly, there was incomplete reporting and significant variation in anti-arrhythmic drug use across studies and we are unable to rule out confounding related to this. Thirdly, given the established discrepancy between treated VTA and aborted sudden death, the absolute rates SCD are likely lower for all subgroups assessed.[34] Fourthly, although the majority of patients examined underwent ICD for primary prevention indication, lack of subgroup analysis limited more robust stratification by ICD indication. Finally, the duration of follow-up across studies was relatively short and longer assessment for ICD therapies are likely warranted to justify change in clinical practice.

Conclusion

Recovery of LVEF post-CRT is associated with significantly reduced appropriate ICD therapy. Patients with recovery of LVEF to ≥45% and those with a primary prevention indication for ICD with LVEF recovery appear to be at lowest risk. A prospective randomized evaluation of the need for continued ICD therapy in patients with LVEF recovery, utilizing standardized ICD programming, may be warranted.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

Study concept and design: N.A.C., A.R., J.P.S., T.M. Acquisition of data: N.A.C., A.R. Analysis and interpretation of data: N.A.C.C., A.R. Critical revision of the manuscript for important intellectual content: N.A.C., A.R., S.A.L., M.R.G., C.D., C.L., J.S., J.P.S., T.M. Statistical Analysis: N.A.C., A.R., S.A.L.

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References

1. Leyva F, Nisam S, Auricchio A. 20 years of cardiac resynchronization therapy. *J Am Coll Cardiol* 2014;**64**:1047–1058.
2. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J. The European cardiac resynchronization therapy survey. *Eur Heart J* 2009;**30**:2450–2460.
3. Garcia-Lunar I, Castro-Urda V, Toquero-Ramos J, Mingo-Santos S, Monivas-Palomero V, Daniela Mitroi C, Sanchez-Garcia M, Perez-Pereira E, Delgado HE, Fernandez-Lozano I. Ventricular arrhythmias in super-responders to cardiac resynchronization therapy. *Rev Esp Cardiol (Engl Ed)* 2014;**67**:883–889.
4. Manfredi JA, Al-Khatib SM, Shaw LK, Thomas L, Fogel RI, Padanilam B, Rardon D, Vatthyam R, Gemma LW, Golden K, Prystowsky EN. Association between left ventricular ejection fraction post-cardiac resynchronization treatment and subsequent implantable cardioverter defibrillator therapy for sustained ventricular tachyarrhythmias. *Circ Arrhythm Electrophysiol* 2013;**6**:257–264.
5. Ruwald MH, Solomon SD, Foster E, Kutyifa V, Ruwald AC, Sherazi S, McNitt S, Jons C, Moss AJ, Zareba W. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. *Circulation* 2014;**130**:2278–2286.
6. Schaer BA, Osswald S, Di Valentino M, Soliman OI, Sticherling C, ten Cate FJ, Jordaens L, Theuns DA. Close connection between improvement in left ventricular function by cardiac resynchronization therapy and the incidence of arrhythmias in cardiac resynchronization therapy-defibrillator patients. *Eur J Heart Fail* 2010;**12**:1325–1332.
7. Sebag FA, Lellouche N, Chen Z, Tritar A, O'Neill MD, Gill J, Wright M, Leclercq C, Rinaldi CA. Positive response to cardiac resynchronization therapy reduces arrhythmic events after elective generator change in patients with primary prevention CRT-D. *J Cardiovasc Electrophysiol* 2014;**25**:1368–1375.
8. Steffel J, Milosevic G, Hurlimann A, Krasniqi N, Namdar M, Ruschitzka F, Luscher TF, Duru F, Holzmeister J, Hurlimann D. Characteristics and long-term outcome of echocardiographic super-responders to cardiac resynchronisation therapy: 'real world' experience from a single tertiary care centre. *Heart* 2011;**97**:1668–1674.
9. Van Boven N, Bogaard K, Ruiter J, Kimman G, Theuns D, Kardys I, Umans V. Functional response to cardiac resynchronization therapy is associated with improved clinical outcome and absence of appropriate shocks. *J Cardiovasc Electrophysiol* 2013;**24**:316–322.
10. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–1118.
11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–2012.
12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;**52**:377–384.
13. Guevara JP, Berlin JA, Wolf FM. Meta-analytic methods for pooling rates when follow-up duration varies: a case study. *BMC Med Res Methodol* 2004;**4**:17.
14. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002;**7**:51–61.
15. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. *Stat Med* 2002;**21**:1513–1524.
16. Lam SK, Owen A. Combined resynchronisation and implantable defibrillator therapy in left ventricular dysfunction: Bayesian network meta-analysis of randomised controlled trials. *BMJ* 2007;**335**:925.
17. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
18. Saxon LA, Bristow MR, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, Feldman AM, Galle E, Ecklund F. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. *Circulation* 2006;**114**:2766–2772.
19. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–1932.
20. Cha YM, Chareonthaitawee P, Dong YX, Kemp BJ, Oh JK, Miyazaki C, Hayes DL, Rea RF, Asirvatham SJ, Webster TL, Dalzell CM, Hodge DO, Herges RM, Yong YZ, Zhang Y, Chen PS. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. *Circ Heart Fail* 2011;**4**:339–344.
21. Di Biase L, Gasparini M, Lunati M, Santini M, Landolina M, Boriani G, Curnis A, Bocchiardo M, Vincenti A, Denaro A, Valsecchi S, Natale A, Padeletti L. Antiarrhythmic effect of reverse ventricular remodeling induced by cardiac resynchronization therapy: the InSync ICD (Implantable Cardioverter-Defibrillator) Italian Registry. *J Am Coll Cardiol* 2008;**52**:1442–1449.
22. Eickholt C, Siekiera M, Kirmanoglou K, Rodenbeck A, Heussen N, Schauerte P, Lichtenberg A, Balzer J, Rassaf T, Perings S, Kelm M, Shin DI, Meyer C. Improvement of left ventricular function under cardiac resynchronization therapy goes along with a reduced incidence of ventricular arrhythmia. *PloS One* 2012;**7**:e48926.
23. Manne M, Rickard J, Varma N, Chung MK, Tchou P. Normalization of left ventricular ejection fraction after cardiac resynchronization therapy also normalizes survival. *Pacing Clin Electrophysiol* 2013;**36**:970–977.
24. Kandala J, Altman RK, Park MY, Singh JP. Clinical, laboratory, and pacing predictors of CRT response. *J Cardiovasc Transl Res* 2012;**5**:196–212.
25. Antonio N, Teixeira R, Coelho L, Lourenco C, Monteiro P, Ventura M, Cristovao J, Elvas L, Goncalves L, Providencia LA. Identification of 'super-responders' to cardiac resynchronization therapy: the importance of symptom duration and left ventricular geometry. *Europace* 2009;**11**:343–349.
26. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. *J Am Coll Cardiol* 2012;**59**:2366–2373.
27. Ghio S, Freemantle N, Scelsi L, Serio A, Magrini G, Pasotti M, Shankar A, Cleland JG, Tavazzi L. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. *Eur J Heart Fail* 2009;**11**:480–488.
28. Kloppe A, Proclemer A, Arenal A, Lunati M, Martinez Ferrer JB, Hersi A, Gulaj M, Wijffels MC, Santi E, Manotta L, Mangoni L, Gasparini M. Efficacy of long detection interval implantable cardioverter-defibrillator settings in secondary prevention population: data from the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE III) trial. *Circulation* 2014;**130**:308–314.
29. Costea A, Rardon DP, Padanilam BJ, Fogel RI, Prystowsky EN. Complications associated with generator replacement in response to device advisories. *J Cardiovasc Electrophysiol* 2008;**19**:266–269.
30. Kleemann T, Becker T, Doenges K, Vater M, Senges J, Schneider S, Saggau W, Weisse U, Seidl K. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of >10 years. *Circulation* 2007;**115**:2474–2480.
31. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;**28**:42–51.
32. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;**359**:1009–1017.
33. Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *J Gen Intern Med* 2008;**23**(Suppl 1):13–19.
34. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol* 2008;**52**:1111–1121.
35. Barsheshet A, Moss AJ, Huang DT, McNitt S, Zareba W, Goldenberg I. Applicability of a risk score for prediction of the long-term (8-year) benefit of the implantable cardioverter-defibrillator. *J Am Coll Cardiol* 2012;**59**:2075–2079.
36. Thijssen J, van Rees JB, Venlet J, Borleffs CJ, Hoke U, Putter H, van der Velde ET, van Erven L, Schalij MJ. The mode of death in implantable cardioverter-defibrillator and cardiac resynchronization therapy with defibrillator patients: results from routine clinical practice. *Heart Rhythm* 2012;**9**:1605–1612.
37. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
38. Jolly S, Dorian P, Alter DA. The impact of implantable cardiac defibrillators for primary prophylaxis in the community: baseline risk and clinically meaningful benefits. *J Eval Clin Pract* 2006;**12**:190–195.
39. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. ACCF/HRS/AHA/ASE/HFSA/SCAI/

SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *Heart Rhythm* 2013;**10**:e11–e58.

40. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, Cerkvenik J, Linde C. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy: analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (REVERSE). *Circ Arrhythm Electrophysiol* 2013;**6**:1163–1168.
41. Morani G, Gasparini M, Zanon F, Casali E, Spotti A, Reggiani A, Bertaglia E, Solimene F, Molon G, Accogli M, Tommasi C, Paoletti Perini A, Ciardiello C, Padeletti L. Cardiac resynchronization therapy-defibrillator improves long-term survival compared with cardiac resynchronization therapy-pacemaker in patients with a class IA indication for cardiac resynchronization therapy: data from the Contak Italian Registry. *Europace* 2013;**15**:1273–1279.

CARDIOVASCULAR FLASHLIGHT

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X-ray-free implantation of a permanent pacemaker during pregnancy using a 3D electro-anatomic mapping system

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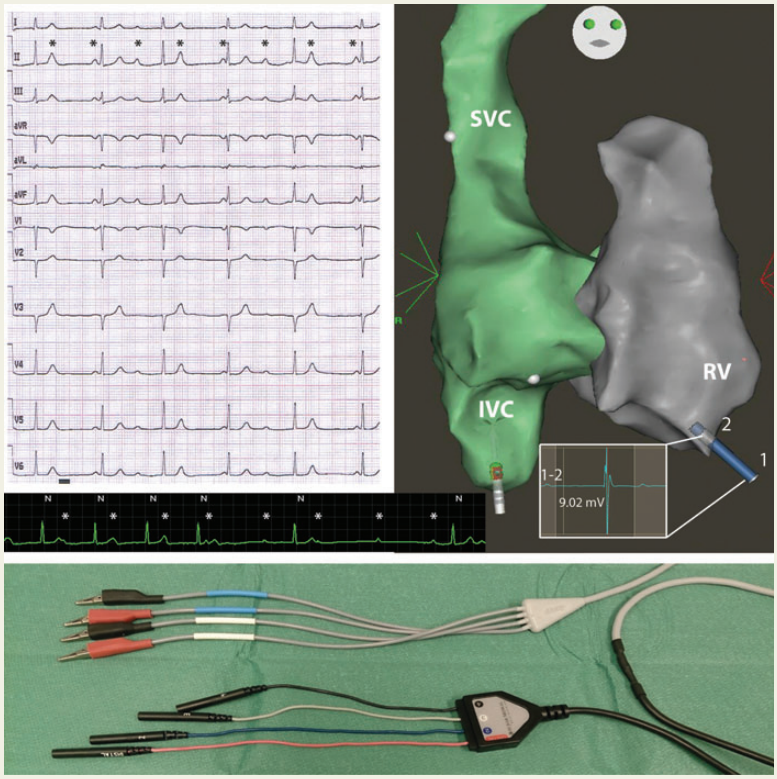
A 30-year-old patient presented with new-onset dizziness and palpitations in her 9th week of gestation. Physical examination revealed cannon waves upon inspection of her jugular veins. Electrolytes were within normal range. A 12-lead electrocardiogram (ECG) showed sinus rhythm at a rate of 94 bpm and complete atrioventricular (AV) block with a junctional escape rhythm at a rate of 60 bpm. No previous ECG was available. In-hospital rhythm monitoring showed repetitive episodes of junctional arrests associated with dizziness. Whereas congenital AV block could not be ruled out, the history suggested a recent onset of the condition. The cause of AV block remained unclear.



Because of the junctional escape rhythm with intermittent arrests and the symptoms, implantation of a permanent pacemaker was recommended. Due to the early stage pregnancy, a fluoroscopy-free approach was desired. For this purpose, a 3D reconstruction of the vena cava, the right atrium, and the right ventricle was performed using an electroanatomic mapping system (CARTO3) and a mapping catheter. A custom-made cable consisting of crocodile clamps was connected to a VDD pacemaker lead and a handle with 2 mm shielded pins was connected to the electroanatomic mapping system. By defining the pacemaker lead as a diagnostic electrophysiologic catheter to be displayed in the mapping system, stable real-time visualization of the pacemaker lead tip (in blue) in 3D from the innominate vein all the way into the apex of the right ventricle was feasible.

Connecting a pacemaker lead to an electroanatomic mapping system is feasible and enables X-ray-free implantation of a permanent pacemaker.